

CLAIMS

520
039,040

1. A crystallization method of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride

which comprises mixing a solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride in a good solvent with an aliphatic
hydrocarbon solvent to crystallize said N-carboxylic anhydride,
the solution of said N-carboxylic anhydride in the good
solvent being added to the aliphatic hydrocarbon solvent to
thereby effect crystallization while inhibiting an oil formation
and scaling of said N-carboxylic anhydride.

2. The crystallization method according to Claim 1
wherein a temperature at addition of the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride in the good solvent to the aliphatic
hydrocarbon solvent is not higher than 60°C.

3. The crystallization method according to Claim 2
wherein the temperature at addition of the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride in the good solvent to the aliphatic
hydrocarbon solvent is -30 to 50°C.

4. The crystallization method according to Claim 3
wherein the temperature at addition of the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride in the good solvent to the aliphatic
hydrocarbon solvent is -20 to 45°C.

5. The crystallization method according to any one of
Claims 1 to 4

wherein the aliphatic hydrocarbon solvent is a saturated

hydrocarbon of 5 to 12 carbon atoms represented by C_nH_{2n+2} or C_nH_{2n} , an unsaturated hydrocarbon of 5 to 12 carbon atoms represented by C_nH_{2n} or C_nH_{2n-2} or a mixed solvent thereof.

5 6. The crystallization method according to Claim 5 wherein the aliphatic hydrocarbon solvent is a saturated hydrocarbon solvent of 5 to 12 carbon atoms represented by C_nH_{2n+2} or C_nH_{2n} or a mixed solvent thereof.

10 7. The crystallization method according to Claim 6 wherein the aliphatic hydrocarbon solvent is pentane, 2-methylpentane, normal hexane, isohexane, normal heptane, normal octane, cyclohexane, methylcyclohexane, ethylcyclohexane, propylcyclohexane or a mixed solvent thereof.

15 8. The crystallization method according to Claim 7 wherein the aliphatic hydrocarbon solvent is normal hexane, isohexane, normal heptane, methylcyclohexane or a mixed solvent thereof.

20 9. The crystallization method according to any one of Claims 1 to 8

wherein the good solvent is a hydrogenated hydrocarbon, an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

25 10. The crystallization method according to Claim 9 wherein the good solvent is dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 30 tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, acetone, methyl ethyl ketone or a mixed solvent thereof.

35

RECEIVED
 1964
 10-10-64
 SUB
 AI


11. The crystallization method according to Claim 9 wherein the good solvent is a halogenated hydrocarbon, an ether, an ester or a mixed solvent thereof.

5 12. The crystallization method according to Claim 11 wherein the good solvent is dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, ethyl
10 acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate or a mixed solvent thereof.

13. The crystallization method according to Claim 11
15 wherein the good solvent is a halogenated hydrocarbon.

14. The crystallization method according to Claim 13 wherein the good solvent is dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane,
20 1,1,1-trichloroethane, 1,1,2-trichloroethane or a mixed solvent thereof.

15. The crystallization method according to Claim 14 wherein the good solvent is dichloromethane.
25

 16. The crystallization method according to any one of Claims 1 to 15 wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
30 N-carboxylic anhydride in the good solvent is carried out by a sequential addition.

17. The crystallization method according to Claim 16 wherein the sequential addition of the solution of
35 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine

wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out in a condition that a crystal of said N-carboxylic anhydride is added to said aliphatic hydrocarbon solvent in advance.

19. The crystallization method according to Claim 18 wherein an amount of the crystal of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride to be added in advance is not more than 30 weight % based on the total amount of said N-carboxylic anhydride in the solution in the good solvent to be subsequently added.

wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out by adding a portion of said solution in the good solvent to said aliphatic hydrocarbon solvent in advance to thereby prepare a slurry in which said N-carboxylic anhydride is precipitated, followed by adding the rest of said solution in a good solvent to said slurry.

21. The crystallization method according to Claim 20 wherein an amount of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to be added in advance

is not more than 30 weight % based on the total amount of the solution in the good solvent to be added.

5 22. The crystallization method according to any one of Claims 1 to 21

wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25°C following completion of the addition.

10 23. The crystallization method according to any one of Claims 1 to 22

wherein a weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.001 to 1.

15 24. The crystallization method according to Claim 23 wherein the weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.003 to 1.

20 25. The crystallization method according to any one of Claims 1 to 24

wherein the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
25 N-carboxylic anhydride in the good solvent is
an NCA forming reaction solution obtained by reacting
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with
N,N'-carbonyldiimidazole or phosgene or
a solution obtained by subjecting the reaction solution
30 to concentration or solvent exchange.

26. The crystallization method according to Claim 25
wherein an impurity or a coloring component as the
byproduct of the NCA forming reaction is removed by using an
35 adsorbent prior to the crystallization.

SUB
A5

1001313-0001

SUB
A6

wherein an NCA forming reaction solvent doubles as the good solvent for the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent.

which comprises adding an aliphatic hydrocarbon solvent to a solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in a good solvent to crystallize
15 said N-carboxylic anhydride,

20 29. The crystallization method according to Claim 28
wherein a temperature at addition of the aliphatic
hydrocarbon solvent to the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
25 N-carboxylic anhydride in the good solvent is -30 to 50°C.

31. The crystallization method according to any one of
Claims 28 to 30
35 wherein the aliphatic hydrocarbon solvent is a saturated

hydrocarbon of 5 to 12 carbon atoms represented by C_nH_{2n+2} or C_nH_{2n} , an unsaturated hydrocarbon of 5 to 12 carbon atoms represented by C_nH_{2n} or C_nH_{2n-2} , or a mixed solvent thereof.

5 32. The crystallization method according to Claim 31 wherein the aliphatic hydrocarbon solvent is a saturated hydrocarbon of 5 to 12 carbon atoms represented by C_nH_{2n+2} or C_nH_{2n} , or a mixed solvent thereof.

10 33. The crystallization method according to Claim 32 wherein the aliphatic hydrocarbon solvent is pentane, 2-methylpentane, normal hexane, isohexane, normal heptane, normal octane, isooctane, normal decane, cyclopentane, cyclohexane, methylcyclohexane, ethylcyclohexane,
15 propylcyclohexane or a mixed solvent thereof.

 34. The crystallization method according to Claim 33 wherein the aliphatic hydrocarbon solvent is normal hexane, isohexane, normal heptane, isooctane, methylcyclohexane or a
20 mixed solvent thereof.

 35. The crystallization method according to any one of Claims 28 to 34
 wherein the good solvent is a halogenated hydrocarbon,
25 an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

 36. The crystallization method according to Claim 35 wherein the good solvent is a halogenated hydrocarbon,
an ether, an ester or a mixed solvent thereof.
30

 37. The crystallization method according to Claim 36 wherein the good solvent is a halogenated hydrocarbon.

 38. The crystallization method according to Claim 35
35 wherein the good solvent is dichloromethane,

204240-8 FEB 1961

SUB
AB

1,1-dichloroethane, 1,2-dichloroethane,
 1,1,1-trichloroethane, 1,1,2-trichloroethane,
 tétrahydrofuran, 1,4-dioxane, t-butyl methyl ether,
 acetonitrile, ethyl acetate, methyl acetate, propyl acetate,
 5 isopropyl acetate, butyl acetate, isobutyl acetate, pentyl
 acetate, methyl propionate, ethyl propionate, acetone, methyl
 ethyl ketone or a mixed solvent thereof.

39. The crystallization method according to Claim 36
 10 wherein the good solvent is dichloromethane,
 1,1-dichloroethane, 1,2-dichloroethane,
 1,1,1-trichloroethane, 1,1,2-trichloroethane,
 tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, ethyl
 acetate, methyl acetate, propyl acetate, isopropyl acetate,
 15 butyl acetate, isobutyl acetate, pentyl acetate, methyl
 propionate, ethyl propionate or a mixed solvent thereof.

40. The crystallization method according to Claim 37
 wherein the good solvent is dichloromethane,
 20 1,1-dichloroethane, 1,2-dichloroethane,
 1,1,1-trichloroethane, 1,1,2-trichloroethane or a mixed
 solvent thereof.

41. The crystallization method according to Claim 40
 25 wherein the good solvent is dichloromethane.

~~42. The crystallization method according to any one of
 Claims 28 to 41~~

~~wherein the addition of the aliphatic hydrocarbon solvent
 30 to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-
 L-alanine N-carboxylic anhydride in the good solvent is carried
 out under stirring with a stirring force corresponding to a
 stirring power requirement of not less than 0.1 kW/m³.~~

35 43. The crystallization method according to Claim 42

201410-8161001

SUB
A9

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out under stirring with the stirring force corresponding to the stirring power requirement of not less than 0.3 kW/m³.

44. The crystallization method according to any one of Claims 28 to 43

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out by preparing a slurry of said N-carboxylic anhydride in advance and adding the aliphatic hydrocarbon solvent sequentially to said slurry.

45. The crystallization method according to Claim 44 wherein a suspension amount of the slurry of said N-carboxylic anhydride to be prepared in advance is not more than 30 weight % based on the total amount of said N-carboxylic anhydride at completion of the crystallization.

46. The crystallization method according to Claim 44 or 45

wherein the preparation of the slurry is carried out by sequential addition of the aliphatic hydrocarbon solvent to the solution of said N-carboxylic anhydride in the good solvent and/or by addition of a crystal of said N-carboxylic anhydride to the solution of said N-carboxylic anhydride in the good solvent.

47. The crystallization method according to Claim 46 wherein the aliphatic hydrocarbon solvent is added to the solution in the good solvent in such a proportion that a weight ratio of the good solvent to the aliphatic hydrocarbon solvent is 0.1 to 10 at a preliminary crystallization.

~~48. The crystallization method according to any one of
Claims 28 to 47~~

5 wherein the weight ratio of the good solvent to the
aliphatic hydrocarbon solvent is 0.001 to 1 at completion of
the addition.

49. The crystallization method according to Claim 48
wherein the weight ratio of the good solvent to the
10 aliphatic hydrocarbon solvent is 0.003 to 0.8 at completion of
the addition.

~~50. The crystallization method according to any one of
Claims 28 to 49~~

15 wherein an amount of a precipitated crystal is increased
by adjusting a liquid temperature to -30 to 25°C following
completion of the addition.

~~51. The crystallization method according to any one of
Claims 28 to 50~~

20 wherein the solution of
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
N-carboxylic anhydride in the good solvent is
an NCA forming reaction solution obtained by reacting
25 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with
N,N'-carbonyldiimidazole or phosgene or
a solution obtained by subjecting the reaction solution
to concentration or solvent exchange.

30 52. The crystallization method according to Claim 51
wherein an impurity or a coloring component as a byproduct
of the NCA forming reaction is removed by using an adsorbent
prior to the crystallization.

35 53. The crystallization method according to Claim 51 or

52

~~wherein an NCA forming reaction solvent doubles as the
good solvent for the solution of~~

~~N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine~~

5 N-carboxylic anhydride in the good solvent

SUB
A19 cont.

10010310 044000